In the Specification

Please substitute the following title:

~~HUMAN cDNAs AND PROTEINS AND USES THEREOF~~

CYTOGRAM POLYPEPTIDES AND USES THEREOF

Please substitute the following paragraphs:

[0276] Lectir is a polymorphic variant of the C-type Lectin-like receptor 2 (GenBank accession number AAF36777). Lectir possesses an anchor signal, a transmembrane domain (VMALILLILCVGMVVGLVALGIW) (SEQ ID NO:53), a lectin C-type domain (QYCTDMNATLLKIDNRNIVEYIKARTHLIRWVGLSRQKSNEVWKWEDGSVISENMFEFL EDGKGNMNCAYFHNGKMHPTFCENKHYLMCE) (SEQ ID NO:54) and an extracellular link domain (RHNLTWEESKQYCTDMNATL) (SEQ ID NO:55). Lectir is homologous to the oxidized LDL receptor (LOX-1). Lectir is expressed in myeloid cells such as monocytes, dendritic cells and granulocytes.

[0290] Preferred vlADAM20 polypeptides for uses in the methods described below include the polypeptides comprising the amino sequence of: MVQLHQDTDPQIPKGQPCTLNSSEGGAR PAVPHTLFSSALDRWLHNDSFI (SEQ ID NO:56).

[0292] vlADAM20 is a sperm protein that is a member of the ADAM family, and that displays all structural elements that are characteristic of this family. Notably, vlADAM20 displays a catalytic site of an active Zn^{2+}- metalloprotease (HELGHNLGMQHD) (SEQ ID NO:57), one disintegrin consensus sequence (EEGEECDCG) (SEQ ID NO:58) and one transmembrane domain. The ADAM family of proteins contains a disintegrin and metalloproteinase domain. Members of

this family are cell surface proteins with a unique structure possessing both potential adhesion and protease domains. Although all ADAMs have the same domain organization, members of the ADAM do not all display the same functions. The functions displayed by members of the ADAM family are regulated by processes that include alternative splicing, differential gene expression, dimerization, and proteolytic processing. ADAMs are involved in diverse biological processes such as spermatogenesis, fertilization, myoblast fusion and neuron proliferation (Wolfsberg *et al*, Dev Biol. 180:389-401 (1996)).

[0298] A further embodiment of the invention is directed to an antibody or an antigen-binding fragment that binds to a vlADAM20 polypeptide or against a vlADAM20 polypeptide fragment. Preferably, the antibody specifically binds to the vlADAM20 polypeptide and not to the ADAM20 polypeptide. Preferably, the antibody or antigen-binding fragment recognizes an epitope comprising one or more of the 50 amino-acids located at the amino-terminal extremity of vlADAM20, wherein one or more of these amino-acids are required for antibody binding. Even more preferably, the antibody recognizes the QLHQDTDPQIPKGQPCT (SEQ ID NO:59) amino-acid sequence or the LNSSEGGAR (SEQ ID NO:60) amino-acid sequence. As used herein, the term *anti-vlADAM20 antibody* includes both intact molecules as well as active fragments thereof, such as those capable of binding antigens.

[0329] The protein of SEQ ID NO:10, PBK, is a splice variant of the sequence of 3-Ketoacyl-CoA Thiolase protein (swissprot accession number P09110). The 153 amino acid protein of PBK displays one membrane-spanning segment: CSSGLQAVASIAGWSPCPWLT (SEQ ID NO:61). Accordingly, some embodiments of the present invention relate to polypeptides comprising the transmembrane domain. Finally, the protein of the invention displays a thiolase domain spanning the sequence: APQASAADVVVVHGRRTAICRAGRGGFKDTTPDELLSAVMTAVLKDVNLRPE QLGDICVGNVLQPGAGAIMARIAQFLSDIPETVPLSTVNRQCSSGLQAVASIAGWSPCPWL TEGTLEIL (SEQ ID NO:62). Accordingly, a preferred embodiment of the present invention comprises the amino acids of the thiolase domain and polynucleotides encoding the same.

[0349] The protein of the present invention, myeloidin, is a novel splice variant of the brain OX-2 protein (Genbank accession number P41217). Myeloidin is 262 amino acids long. OX-2 is 274 amino-acids long and differs from myeloidin at both the amino-terminal and the carboxyl-terminal extremities. Another known splice variant of OX-2, my033, is 269 amino acids long and differs from myeloidin at the amino-terminal extremity. Myeloidin displays a signal peptide (MPFSHLSTYSLVWVMAAVVLCTA) (SEQ ID NO:63), one transmembrane domain (VPLLLSIVSLVILLVLISILLYW) (SEQ ID NO:64) and two immunoglobulin (Ig) domains (TASLKCSLQNAQEALIVTWQKKKAVSPENMVTFSENHGVVIQPAYKDKINITQLGLQNS TITFWNITLEDEGCYMCLF (SEQ ID NO:65) and EDHLNITCSATARPAPMVFWKVPRSGIEN STVTLSHPNGTTSVTSILHIKDPKNQVGKEVICQV) (SEQ ID NO:66). Myeloidin is expressed by a wide variety of cells, including those of the central nervous system (CNS).

[0402] The protein of SEQ ID NO:18, BZRP-R3, is a novel polymorphic variant of human peripheral benzodiazepine receptor/isoquinoline binding protein (PBR/IBP) (accession numbers Q9Y531). BZRP-R3 displays five transmembrane-spanning segments: LQGAIFVLLPHLGPILVWLFT (SEQ ID NO:67), VLLLVQTAIYSVVGYASYLVW (SEQ ID NO:68), GLYADQLTISWTVLVLFFTVH (SEQ ID NO:69), GLALLHLLLLYGLVVSTALIW (SEQ ID NO:70), and LAALLLLPYLAWLTVTSALTY (SEQ ID NO:71). Accordingly, some embodiments of the present invention relate to polypeptides comprising the transmembrane domains. Moreover, BZRP-R3 displays a stretch of 11 amino acids (VTSALTYHLWR) (SEQ ID NO:72) that bind cholesterol. Accordingly, a preferred embodiment of the present invention comprises the amino acids of the cholesterol recognition/interaction domain and the polynucleotides encoding the same.

[0429] The protein of SEQ ID NO:20, BZRP-R4, is a novel polymorphic variant of human peripheral benzodiazepine receptor/isoquinoline binding protein (PBR/IBP) (accession numbers Q9Y531). BZRP-R4 displays five transmembrane-spanning segments:

LQGAIFVLLPHLGPILVWLFT (SEQ ID NO: 67), VLLLVQTAIYSVVGYASYLVW (SEQ ID NO:68), LYAVQLTISWTVLVLFFTVHN (SEQ ID NO:73), LALLHLLLLYGLVVSTALIWH (SEQ ID NO:74), and LAALLLLPYLAWLTVTSALTY (SEQ ID NO:71). Accordingly, some embodiments of the present invention relate to polypeptides comprising the transmembrane domains. Moreover, BZRP-R4 displays a stretch of 11 amino acids (VTSALTYHLWR) (SEQ ID NO:72) that bind cholesterol. Accordingly, a preferred embodiment of the present invention comprises the amino acids of the cholesterol recognition/interaction domain and the polynucleotides encoding the same.

[0483] A preferred embodiment of the invention includes an excitation-secretion uncoupling peptide (ESUP). Preferred DOV ESUPs include the peptide sequences: LLHNHLTVRVIEARDL PPPISHDGSRQDMAHSNPYVKICLLPDQKNSKQTGVKRKTQKPVFEERYTFEIPFLEAQRR TLLLTVVDFDKFSRHCVIGKVS (SEQ ID NO:75); GRLNVDVIRAKQLLQTDVSQGS DPFVKIQLVHGLKLVKTKKTSFLRGTIDPFYNESFSFKVPQEELENASLVFTVFGHNMKSS NDFIGRIVIG (SEQ ID NO:76); and effective ESUP fragments of said peptides.

[0493] DOV polypeptides are also useful in methods of inhibiting the release of neurotransmitters by preventing the docking and/or fusing of a presynaptic vesicle to the presynaptic membrane. These polypeptides may be referred to as excitation-secretion uncoupling peptides (ESUPs). Fragments of DOV having this blocking activity can be identified using methods known in the art (See e.g., U.S. Patents 6,090,631 and 6,169,074 incorporated by reference in their entireties). ESUPs of the present invention comprise synthetic and purified DOV peptide fragments which correspond in primary structure to peptides which serve as binding domains for the assembly of a ternary protein complex ("docking complex") which is critical to neuronal vesicle docking with the cellular plasma membrane prior to neurotransmitter secretion. For optimal activity, ESUPs of the invention have a minimum length of about 20 amino acids and a maximal length of about 100 amino acids, although they may be larger or smaller. Preferred DOV ESUPs for use in inhibiting the release of neurotransmitters include those comprising the sequence: LLHNHLTVRVIEARDLPPPISHD GSRQDMAHSNPYVKICLLPDQKNSKQTGVKRKTQKPVFEERYTFEIPFLEAQRRTLLLTV

VDFDKFSRHCVIGKVS (SEQ ID NO:75); GRLNVDVIRAKQLLQTDVSQGSDPFVKI QLVHGLKLVKTKKTSFLRGTIDPFYNESFSFKVPQEELENASLVFTVFGHNMKSSNDFIGR IVIG (SEQ ID NO:76); and effective ESUP fragments of said peptides. DOV ESUPs are preferably covalently linked to a targeting moiety. Preferred targeting moieties comprise a ligand to a cell-surface binding site present on a specific cell type (e.g., neuron) that is capable of functionally interacting with the binding site. Preferred targeting moieties are nerve growth factor and functional derivatives thereof. Alternatively, DOV ESUPs may be expressed in a cell by introducing polynucleotides encoding DOV ESUPs to the cell. Methods of introducing polynucleotides to a cell are known to those skilled in the art, as discussed herein and in U.S. Patents 6117454 and 6180602, which disclosures are hereby incorporated by reference in their entireties.

[0499] The cDNA of Clone 500706437_204-5-2-0-C9-F (SEQ ID NO:25) encodes placentalin of SEQ ID NO:26, comprising the amino acid sequence: MDPARPLGLSILLLFLTEAA LGDAAQEPTGNNAEICLLPLDYGPCRALLLRYYYDRYTQSCRQFLYGGCEGNANNFYTW EACDDLAGG. Accordingly, it will be appreciated that all characteristics and uses of the polypeptides of SEQ ID NO:26 described throughout the present application also pertain to the polypeptides encoded by the nucleic acids comprising the human cDNA in Clone 500706437_204-5-2-0-C9-F . In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NO:25 described throughout the present application also pertain to the nucleic acids included in Clone 500706437_204-5-2-0-C9-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:26, SEQ ID NO:25, and Clone 500706437_204-5-2-0-C9-F . Preferred placentalin polypeptides for uses in the methods described below include the polypeptides comprising the amino sequence of: AQEPTGNNAEICLLPLDYGPCRALLL RYYYDRYTQSCRQFLYGGCEGNANNFYTWEACDDLAGG (SEQ ID NO:77). Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

[0500] The protein of the present invention, placentalin, is a variant of the Tissue Factor Pathway Inhibitor 2 (TFPI-2, GenBank accession number P48307). The 84 amino-terminal amino-acids are identical between TFPI-2 and placentalin, and the 4 carboxyl-terminal amino-acids are unique to placentalin. Placentalin displays one signal peptide (MDPARPLGLSILLLFLTEAALGDA) (SEQ ID NO:78) and one Kunitz inhibitor domain (CLLPLDYGPCRALLLRYYYDRYTQSCRQFLYGGCEGNANNFYTWEACDDLA) (SEQ ID NO:79). Placentalin lacks the main heparin-binding site, located at the carboxyl-terminal extremity of TFPI-2. A wide variety of cell types, including endothelial cells, keratinocytes and fibroblasts, synthetize and secrete placentalin under normal conditions. Moreover, placentalin is highly expressed in umbilical vein endothelial cells and its expression level negatively correlates with malignancy-grade of tumors.

[0531]

MAAVLTWALALLSAFSATQARKGFWDYFSQTSGDKGRVEQIHQQKMAREPATLK
DSLEQDLNNMNKFLEKLRPLSGSEAPRLPQDPVGMRRQLQEELEEVKARLQPYMAEAHE
LVGWNLEGLRQQLKPYTMDLMEQVALRVQELQEQLRVVGEDTKAQLLGGVDEAWALL
QGLQSRVVHHTGRFKELFHPYAESLVSGIGRHVQELHRSVAPHAPASPARLSRCVQVLSR
KLTLKAKALHARIQQNLD (SEQ ID NO:80). Accordingly, an embodiment of the present invention comprises the amino acids of the apolipoprotein motif and the polynucleotides encoding the same.

[0555] The protein of SEQ ID NO:29, Neurexinal, is a splice variant of Neurexin I-alpha protein (Genbank accession number AB035356). The protein of the invention displays a G-Laminin motif: FKTLQRNGLMLHTGKSADYVNLALKNGAVSLVINLGSGAFEALVEPVNGKFNDNAW
HDVKVTRNLRQVTISVDGILTTTGYTQEDYTMLGSDDFFYVGGSPSTADLP (SEQ ID NO:81). Accordingly, some embodiments of the present invention comprise the amino acids of the G-Laminin motif and the polynucleotides encoding the same.

[0562] A further embodiment of the invention is directed to a composition comprising a polynucleotide sequence encoding a Neurexinal polypeptide fragment having biological activity of binding alpha-latrotoxin, neurexophilin, or dystroglycan.

[0577] The protein of SEQ ID NO:32, NPIASY, is a novel polymorphic variant of Protein Inhibitor of Activated STAT Protein (PIASY) (accession numbers O75926). The protein of the invention displays a SAP domain: VMSFRVSDLQMLLGFVGRSKSGLK HELVTRALQLV (SEQ ID NO:82). In addition, NPIASY displays a MIZ Zinc finger motif:

[0578] VSLICPLVKMRLSVPCRAETCAHLQCFDAVFYLQMNEKETCAHLQCFDAVFY LQMNEK (SEQ ID NO:83).

[0603] The cDNA of SEQ ID NO:33 is a novel polymorphic variant of the human chymotrypsin-like protease CTRL-1 encoded by a gene located on chromosome 16, specifically at position 16q22.1. The 264 amino-acid protein of vCRTL-1 contains a signal peptide (MLLLSLTLSLVLLGSSWG) (SEQ ID NO:84) and a serine protease domain and belongs to the serine protease family.

[0609] A further embodiment of the invention is directed to a composition comprising an antibody directed against the vCRTL-1 polypeptide sequence of SEQ ID NO: 34 or a vCRTL-1 polypeptide fragment having a biological activity of protein substrate binding or serine protease activity. Preferably, the antibody specifically binds to vCRTL-1 but not to CTRL-1. Even more preferably, the antibody recognizes the SLQDSSDFHF (SEQ ID NO:85) amino-acid sequence.

[0625] LIRION, the protein of SEQ ID NO:36, represents a novel variant form of the ILT-3

receptor precursor (Genbank entry U82979) starting with a 259 amino acid long extracellular domain including a peptide signal sequence (MIPTFTALLCLGLSLGPRTHMQA) (SEQ ID NO:86) and two C2 type immunoglobulin-like-domains, followed by a transmembrane region (VLIGVLVVSILLLSLLLFLLL) (SEQ ID NO:87) and a 167 amino acid long intracellular domain which contains three Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIMs).

[0629] Preferred LIRION polypeptides for use in the methods described below include the polypeptides comprising the amino sequence of:

GPLPKPTLWAEPGSVISWGNSVTIWCQGTLEAREYRLDKEESPAPWDRQNPLEPKNKARF
SIPSMTEDYAGRYRCYYRSPVGWSQPSDPLELVMTGAYSKPTLSALPSPLVTSEKSVTLLC
QSRSPMDTFLLIKERAAHPLLHLRSEHGAQQHQAEFPMSPVTSVHGGTYRCFSSHGFSHY
LLSHPSDPLELIVSGSLEDPRPSPTRSVSTAAGPEDQPLMPTGSVPHSGLRRHWEVLIGVLV
VSILLLSLLLFLLLQHWRQGKHRTLAQRQADFQRPPGAAEPEPKDGGLQRRSSPAADVQG
ENFCAAVKDTQPEDGVEMDTRSPHDEDPQAVTYAKVKHSRPRREMASPPSPLSGEFLDT
KDRQAEEDRQMDTEAAASEAPQDVTYAQLHSFTLRQKATEPPPSQEGASPAEPSVYATL
AIH (SEQ ID NO:88);

[0630] A polypeptide comprising the amino acid sequence of:

GPLPKPTLWAEPGSVISWGNSVTIWCQGTLEAREYRLDKEESPAPWDRQNPLEPKNKARF
SIPSMTEDYAGRYRCYYRSPVGWSQPSDPLELVMTGAYSKPTLSALPSPLVTSEKSVTLLC
QSRSPMDTFLLIKERAAHPLLHLRSEHGAQQHQAEFPMSPVTSVHGGTYRCFSSHGFSHY
LLSHPSDPLELIVSGSLEDPRPSPTRSVSTAAGPEDQPLMPTGSVPHSGLRRHWE (SEQ ID
NO:89).

[0631] A polypeptide comprising the amino acid sequence of:

QHWRQGKHRTLAQRQADFQRPPGAAEPEPKDGGLQRRSSPAADVQGENFCAAV KDTQPEDGVEMDTRSPHDEDPQAVTYAKVKHSRPRREMASPPSPLSGEFLDTKDRQAEE DRQMDTEAAASEAPQDVTYAQLHSFTLRQKATEPPPSQEGASPAEPSVYATLAIH (SEQ ID NO:90).

[0639] In one embodiment, a sequence encoding SEQ ID NO:36 bearing G to A, G to A and A to G substitutions at nucleotide positions 447, 705 and 1040 of SEQ ID NO:35 corresponding to positions 137, 223 and 335, and resulting in the substitution of a glycine residue by a glutamic acid at position 137, a glycine by an aspartic acid at position 223 and an asparagine residue by an aspartic acid at position 335, respectively, can be used for DNA genotyping. Genotyping this locus could be of interest, e.g., in DNA fingerprinting for paternity studies or forensic analyses. It could also be used for genetic association studies, especially in pathologies relating to B cell autoimmune disorders (e.g., rheumatoid arthritis and ulcerative colitis) and antigen presentation disorders (such as bare lymphocyte syndrome).

[0655] SLAMP, the protein of SEQ ID NO:38, represents a novel splice variant of the limbic system-associated membrane protein (LAMP; Swissprot entry Q13449). SLAMP has a 22 amino acid signal sequence (MRTYWLHSVWVLGFFLSLFSLQ) (SEQ ID NO:91), three C2-type immunoglobulin-like-domains, and a unique 80 amino acid carboxy-terminus. The protein belongs to the IgLON family, a group of neuronal glycoproteins which have been isolated from chicken, rat and human. These include the LAMP protein, Neurotrimin/CEPU-1, OBCAM and kilon/Neurotractin polypeptides. Most of the known members of this family are cell-surface adhesion molecules with a glycosyl phosphatidylinositol anchor at their C-terminus which tethers them to the neuronal plasma membrane. SLAMP, however, lacks the GPI anchor and is thus secreted by neurons in cortical and subcortical regions of the limbic system. SLAMP interacts with itself and other IgLON proteins and is involved in cell-cell recognition, contact-dependent regulation of neurite out-growth and axon guidance of specific subset of neurons during brain development.

SLAMP interacts with LAMP, Neurotrimin and OBCAM, promotes neurite outgrowth of limbic neurons and inhibits neurite outgrowth of non-limbic neurons both in vivo and in vitro.

[0656] Preferred SLAMP polypeptides for uses in the methods described below include the polypeptides comprising the amino sequence of:

GLPVRSVDFNRGTDNITVRQGDTAILRCVVEDKNSKVAWLNRSGIIFAGHDKWSLDPRVE LEKRHSLEYSLRIQKVDVYDEGSYTCSVQTQHEPKTSQVYLIVQVPPKISNISSDVTVNEGS NVTLVCMANGRPEPVITWRHLTPTGREFEGEEEYLEILGITREQSGKYECKAANEVSSADV KQVKVTVNYPPTITESKSNEATTGRQASLKCEASAVPAPDFEWYRDDTRINSANGLEIKST EGQSSLTVTNVTEEHYGNYTCVAANKLGVTNASLVLFKRVLPTIPHPIQEIGTTVHFKQKG IFLSESQRGETTKITLNCGNLFLRNLHPTSDQEPQRLWTLCCLLPRKGQHRIYGQC (SEQ ID NO:92);

[0657] A polypeptide comprising the amino acid sequence of:

GLPVRSVDFNRGTDNITVRQGDTAILRCVVEDKNSKVAWLNRSGIIFAGHDKWSLDPRVE LEKRHSLEYSLRIQKVDVYDEGSYTCSVQTQHEPKTSQVYLIVQVPPKISNISSDVTVNEG SNVTLVCMANGRPEPVITWRHLTPTGREFEGEEEYLEILGITREQSGKYECKAANEVSSAD VKQVKVTVNYPPTITESKSNEATTGRQASLKCEASAVPAPDFEWYRDDTRINSANGLEIKS TEGQSSLTVTNVTEEHYGNYTCVAANKLGVTNASLVLF (SEQ ID NO:93);

[0658] A polypeptide comprising the amino acid sequence of:

KRVLPTIPHPIQEIGTTVHFKQKGIFLSESQRGETTKITLNCGNLFLRNLHPTSDQEPQRLW TLCCLLPRKGQHRIYGQC (SEQ ID NO:94).

[0676] The cDNA of Clone 495718_160-26-2-0-E12-F (SEQ ID NO: 39) encodes SAP-MU-10 of SEQ ID NO:40, comprising the amino acid sequence: MYALFLLASLLGAALAGP VLGLKECTRGSAVWCQNVKTASDCGAVKHCLQTVWNKPTVKSLPCDICKDVVTAAGDM LKDNATEEEILVYLEKTCDWLPKPNMSASCKEIVDSYLPVILDIIKGEMSRPGEVCSALNLC ESLQKHLAELNHQKQLESNKIPELDMTEVVAPFMANIPLLLYPQDGPRSKPQPKDNGDVC QDCIQMVTDIQTAVRTNSTFVQALVEHVKEECDRLGPGMADICKNYISQYSEIAIQMMMH MQDQQPKEICALVGFCDEVKEMPMQTLVPAKVASKNVIPALELVEPIKKHEVPAKSDVYC EVCEFLVKEVTKLIDNNKTEKEILDAFDKMCSKLPKSLSEECQEVVDTYGSSILSILLEEVSP ELVCSMLHLCSGTRLPALTVHVTQPKDGGFCEVCKKLVGYLDRNLEKNSTKQEILAALEK GCSFLPDPYQKQCDQFVAEYEPVLIEILVEVWILPSCA. Accordingly, it will be appreciated that all characteristics and uses of the polypeptides of SEQ ID NO:40 described throughout the present application also pertain to the polypeptides encoded by the nucleic acids comprising the human cDNA in Clone 495718_160-26-2-0-E12-F. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NOs:39 described throughout the present application also pertain to the nucleic acids comprising the human cDNA in Clone 495718_160-26-2-0-E12-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:40, SEQ ID NO:39, and Clone 495718_160-26-2-0-E12-F. Preferred SAP-MU-10 polypeptide fragment for uses in the methods described below include the Sap-D10 polypeptide comprising the amino sequence of: DGGFCEVCKKLVGYLDRNLEKNSTKQEILA ALEKGCSFLPDPYQKQCDQF VAEYEPVLIEILVEVWILPSCA (SEQ ID NO:95). Also preferred are polypeptide fragments comprising the seven C-terminal amino acids, having a biological activity as described herein and the polynucleotides encoding the fragments.

[0689] Additional aspects of this embodiment include methods of using SAP-MU-10 polypeptides to detect and quantify sphingolipids and gangliosides using techniques common in the art. Such methods comprise the steps of: i) obtaining a biological sample suspected of containing sphingolipids or gangliosides; ii) contacting such sample with a SAP-MU-10 polypeptide under conditions allowing binding of SAP-MU-10; and iii) detecting the presence or absence of

sphingolipids and gangliosides by detecting SAP-MU-10. Preferably, the SAP-MU-10 polypeptide is covalently attached to a detectable compound (e.g., enzymatic substrates, or fluorescent, luminescent, and radioactive compounds) ~~(E.G....)~~. Alternatively, a detectable SAP-MU-10-specific antibody may be used to detect SAP-MU-10. This embodiment is useful, for example, as a diagnostic tool for quantifying the amount of sphingolipids in cerebrospinal plasma. Such diagnostic tool may be useful to diagnose sphingolipidosis and various lysosomal storage disorders (LSDs) such as, e.g., cystinosis, Gaucher's disease, multiple sulfatase deficiency, Niemann-Pick disease, Pompe's disease and Wolman's disease.

[0702] The cDNA of Clone 612386_187-9-4-0-B2-F (SEQ ID NO: 41) encodes cytogram of SEQ ID NO:42, comprising the amino acid sequence: MELCRSLALLGGSLGLMFC LIALSTDFWFEAVGPTHSAHSGLWPTGHGDIISGHGPLVSTTAAFAAGKDSGLDWGIASQR IPAEELSHLSCPCPQPSPWWWPWRCTPASGGTSLHTPRSRPSSPGPSTWAGSQLSSCSVQVP (SEQ ID NO:96). Accordingly, it will be appreciated that all characteristics and uses of the polypeptides of SEQ ID NO:42 described throughout the present application also pertain to the polypeptides encoded by the nucleic acids comprising the human cDNA in Clone 612386_187-9-4-0-B2-F. In addition, it will be appreciated that all characteristics and uses of the polynucleotides of SEQ ID NOs:41 described throughout the present application also pertain to the nucleic acids included in Clone 612386_187-9-4-0-B2-F. A preferred embodiment of the invention is directed toward the compositions of SEQ ID NO:42, SEQ ID NO:41, and Clone 612386_187-9-4-0-B2-F. Preferred cytogram polypeptides for uses in the methods described below include the polypeptides comprising the amino sequence of: AHSGLWPTGHGDIISGHGPLVSTTAAFAAGKDSGLD WGIASQRIPAEELSHLSCPCPQPSPWWWPWRCTPASGGTSLHTPRSRPSSPGPSTWAGSQL SSCSVQVP (SEQ ID NO:97). Also preferred are polypeptide fragments having a biological activity as described herein and the polynucleotides encoding the fragments.

[0703] The protein of the invention, cytogram, is a splice variant of GMP-17 (or NKG7, GenBank accession number Q16617). Cytogram cDNA lacks the second exon of GMP-17 cDNA.

Cytogram is a 142 amino-acid long protein, and GMP-17 is 165 amino acid long. The 53 amino-terminal amino acids are identical between the two proteins, and the 89 carboxyl-terminal amino acids are unique to cytogram. Cytogram displays a signal peptide (MELCRSLALLGGSLGLMFCLIALSTDFWFEAVGPTHS) (SEQ ID NO:98), a transmembrane domain (GDIISGHGPLVSTTAAFAAGK) (SEQ ID NO:99), and a PEC family methallothionein domain (SCPCPQPSPWWWPWRCTPASGGTSLHTPRSRPSSPGPSTWAGS QLSSCSV) (SEQ ID NO:100) that binds to zinc ions.

[0709] A further embodiment of the invention is directed to a composition comprising an antibody recognizing a cytogram polypeptide sequence of SEQ ID NO:42 or a cytogram polypeptide fragment having biological activity. Preferably, the antibody recognizes a non-linear epitope or an epitope located within the 89 C-terminal amino acids of cytogram. Preferably, the antibody binds to cytogram but not to GMP-17. Preferably, the antibody recognizes the AGKDSGLD (SEQ ID NO:101) amino acid sequence.

[0714] Another embodiment relates to a method of producing cytogram polypeptides comprising the steps of: i) obtaining a cell capable of expressing a cytogram polypeptide; ii) growing said cell under conditions suitable to produce said polypeptide; and iii) purifying said polypeptide. The purification of the protein can be done following any technique well-known to those skilled in the art. Preferably, an antibody directed against cytogram or part thereof may be bound to a chromatographic support to form an affinity chromatography column. Even more preferably, the antibody binds to cytogram but not to GMP-17. The cell capable of expressing a cytogram polypeptide may be obtained by any of the techniques well-known to those skilled in the art. A host cell may be transfected with a recombinant expression vector comprising a polynucleotide of the present invention. Alternatively, ~~an~~ heterologous ~~promotor~~ promoter may be used. Preferably, the host cell is a mammalian host cell.

[0726] The protein of the invention, Tetranab, is a variant of CD37 (GenBank accession number P11049). CD37 is a molecular facilitator that brings together molecular complexes necessary for T-cell dependant B-cell response. CD37 stabilizes molecular interactions, resulting in a more efficient response. Tetranab is a divergent member of the tetraspanin family, which displays one signal anchor (FNLFFFVLGSLIFCFGIWILI) (SEQ ID NO:102) and two transmembrane domains (VLAISGIFTMGIALLGCVGAL (SEQ ID NO:103) and LYFGMLLLLFATQITLGILIS) (SEQ ID NO:104). Tetranab is specifically expressed on mature B cells. It is not expressed during differentiation of B cells and its expression is down-regulated with activation of B cells. Tetranab acts as a dominant negative inhibitor of CD37-facilitated assembly of functional complexes at B cells surfaces. Thus Tetranab prevents CD37-dependent activation of B cells.

[0748] The protein of SEQ ID NO:46, PDI, is a polymorphism variant of protein disulfide isomerase A3 precursor (accession numbers U42068). The protein of the invention displays two thioredoxin domain:

ASDVLELTDDNFESRISDTGSAGLMLVEFFAPWCGHCKRLAPEYEAAATRLKGIVPLAKV DCTANTNTCNKYGVSGYPTLKIFRDGEEAGAYDGPRTADGIVSHLKKQAG (SEQ ID NO:105); and

DGPVKVVVAENFDEIVNNENKDVLIEFYAPWCGHCKNLEPKYKELGEKLSKDP NIVIAKMDATANDVPSPYEVRGFPTIYFSPANKKLNPKKYEGGRELSDFISYLQREAT (SEQ ID NO:106). Also, the 505 amino acid protein of PDI displays one membrane-spanning segment: SDTGSAGLMLVEFFAPWCGHC (SEQ ID NO:107).

[0791] NBTG is a novel polymorphism variant of B-cell translocation gene 1 protein (accession numbers P31607). The protein of the invention displays an anti-proliferative domain:

IGEIAAAVSFISKFLRTKGLTSERQLQTFSQSLQELLAEHYKHHWFPEKPCKGSGYR CIRINHKMDPLIGQAAQRIGLSSQELFRLLPSELTLWVDPYEVSYRIGEDGSICVLYEASPAG GSTQNSTNVQMVDSRISCKEELLLGRTSPSKNYNMMTVSS (SEQ ID NO:108). Accordingly,

some embodiments of the present invention relate to polypeptides comprising the anti-proliferative domain.

[0819] A further embodiment of the invention is directed to a composition comprising an antibody directed against a vITH1 polypeptide sequence of SEQ ID NO: 52 or a vITH1 polypeptide fragment having a biological HA-binding protein activity. Preferably, the antibody specifically binds to vITH1 but not to ITH1. Preferably, the antibody specifically recognizes an epitope comprising the amino acids: VTGG (SEQ ID NO:109), TGGF (SEQ ID NO:110), GGFS (SEQ ID NO:111), VTGGFS (SEQ ID NO:112), MPLP (SEQ ID NO:113), PLPL (SEQ ID NO:114), PLPS (SEQ ID NO:115), LPSA (SEQ ID NO:116), or MPLPLPSA (SEQ ID NO:117).

[0827] The cDNA of Accession No. AAB30232 comprising the nucleotide sequence:

GGAAAACTATGCCTGGGGCCGACGCTCTGCCCGGCTGCTGCCGCTGAGGAAAGCCGG
GACGCGGAGCCCCGCCGAGAGCTTCTTTGCTCCGGACGCCCCTGGACGTGGCGGGCAG
CCGCGAGGGTAACCACCATGATCCCCTGGGTGCTCCTGGCCTGTGCCCTCCCCTGTGC
TGCTGACCCACTGCTTGGCGCCTTTGCTCGCAGGGACTTCCGGAAAGGCTCCCCTCAA
CTGGTCTGCAGCCTGCCTGGCCCCCAGGGCCCACCCGGCCCCCCAGGAGCCCCAGGGC
CCTCAGGAATGATGGGACGAATGGGCTTTCCTGGCAAAGACGGCCAAGATGGACACG
ACGGCGACCGGGGGGACAGCGGAGAGGAAGGTCCACCTGGCCGGACAGGTAACCGG
GGAAAGCCAGGACCAAAGGGCAAAGCCGGGGCCATTGGGCGGGCTGGCCCCCGTGGC
CCCAAGGGGGTCAACGGTACCCCCGGGAAGCATGGCACACCAGGCAAGAAGGGGCCC
AAGGGCAAGAAAGGGGAGCCAGGCCTCCCAGGCCCCTGCAGCTGTGGCAGTGGCCAT
ACCAAGTCAGCTTTCTCGGTGGCAGTGACCAAGAGCTACCCACGGGAGCGGCTGCCCA
TCAAGTTTGACAAGATTCTGATGAACGAGGGTGGCCACTACAATGCTTCCAGCGGCAA
GTTCGTCTGCGGCGTGCCTGGGATCTACTACTTCACCTACGACATCACGCTGGCCAAC
AAGCACCTGGCCATCGGCCTGGTGCACAACGGCCAGTACCGCATCCGGACCTTTGATG

CCAACACCGGCAACCACGATGTGGCCTCAGGCTCCACCATCCTGGCTCTCAAGCAGGG
TGACGAAGTTTGGCTGCAGATCTTCTACTCAGAGCAGAACGGGCTCTTCTATGACCCT
TACTGGACAGACAGCCTCTTTACGGGCTTCCTAATCTATGCCGACCAGGATGACCCCA
ACGAGGTATAGACATGCCACGGCGGTCCTCCAGGCAGGGAACAAGCTTCTGGACTTG
GGCTTACAGAGCAAGACCCCACAACTGTAGGCTGGGGGTGGGGGGTCGAGTGAGCGG
TTCTAGCCTCAGGCTCACCTCCTCCGCCTCTTTTTTTCCCCTTCATTAAATCCAAACCTT
TTTATTCA (SEQ ID NO:118)

[0828] Encodes the protein Acrp30R1L comprising the amino acid sequence:

MIPWVLLACALPCAADPLLGAFARRDFRKGSPQLVCSLPGPQGPPGPPGAPGPSGM
MGRMGFPGKDGQDGHDGDRGDSGEEGPPGRTGNRGKPGPKGKAGAIGRAGPRGPKGVN
GTPGKHGTPGKKGPKGKKGEPGLPGPCSCGSGHTKSAFSVAVTKSYPRERLPIKFDKILMN
EGGHYNASSGKFVCGVPGIYYFTYDITLANKHLAIGLVHNGQYRIRTFDANTGNHDVASGS
TILALKQGDEVWLQIFYSEQNGLFYDPYWTDSLFTGFLIYADQDDPNEV (SEQ ID NO:119).

[0832] The cDNA of Accession No. AAZ45688 comprising the nucleotide sequence

GAATTCGGCACGAGGGCCGCGAGGGTAACCACCATGATCCCCTGGGTGCTCCTGGCC
TGTGCCCTCCCCTGTGCTGCTGACCCACTGCTTGGCGCCTTTGCTCGCAGGGACTTCCG
GAAAGGCTCCCCTCAACTGGTCTGCAGCCTGCCTGGCCCCCAGGGCCCACCCGGCCCC
CCAGGAGCCCCAGGGCCCTCAGGAATGATGGGACGAATGGGCTTTCCTGGCAAAGAC
GGCCAAGATGGACACGACGGCGACCGGGGGGACAGCGGAGAGGAAGGTCCACCTGG
CCGGACAGTGACCAAGAGCTACCCACGGGAGCGGCTGCCCATCAAGTTTGACAAGAT
TCTGATGAACGAGGGTGGCCACTACAATGCTTCCAGCGGCAAGTTCGTCTGCGGCGTGC
CTGGGATCTACTACTTCACCTACGACATCACGCTGGCCAACAAGCACCTGGCCATCGGC
CTGGTGCACAACGGCCAGTACCGCATCCGGACCTTTGATGCCAACACCGGCAACCACGA
TGTGGCCTCAGGCTCCACCATCCTGGCTCTCAAGCAGGGTGACGAAGTTTGGCTGCAGA
TCTTCTACTCAGAGCAGAACGGGCTCTTCTATGACCCTTACTGGACAGACAGCCTCTTTA

CGGGCTTCCTAATCTATGCCGACCAGGATGACCCCAACGAGGTATAGACATGCCACGGC
GGTCCTCCAGGCAGGGAACAAGCTTCTGGACTTGGGCTTACAGAGCAAGACCCCACAA
CTGTAGGCTGGGGGTGGGGGGTCGAGTGAGCGGTTCTAGCCTCAGGCTCACCTCCTCTG
CCTCTTTTTTTCCCCTTCATTAAATCCAAACCTTTTTATTCAAAAAAAAAAAAAAAAAAA
GATGCGGCCG (SEQ ID NO:120)

[0833] Encodes the protein Acrp30R1 comprising the amino acid sequence

MIPWVLLACALPCAADPLLGAFARRDFRKGSPQLVCSLPGPQGPPGPPGAPGPSGMM
GRMGFPGKDGQDGHDGDRGDSGEEGPPGRTVTKSYPRERLPIKFDKILMNEGGHYNASSGK
FVCGVPGIYYFTYDITLANKHLAIGLVHNGQYRIRTFDANTGNHDVASGSTILALKQGDEVW
LQIFYSEQNGLFYDPYWTDSLFTGFLIYADQDDPNEV (SEQ ID NO:121).

[0842] Acrp30R1L and Acrp30R1 are characterized by an amino acid motif that is otherwise specific for chemokine SLC, as determined by BLAST analysis of the public protein database. The specificity of this motif for SLC extends across species. The motif, encompassing amino acids 21 to 46 of Acrp30R1L and Acrp30R1 (and therefore N-terminal to the putative protease cleavage sites within Acrp30R1L and Acrp30R1) is: RxxRKxxPxLxCSxP (SEQ ID NO:122) (where "x" is an unassigned amino acid). This specific motif is conserved between human (Accession Nos. AAY12316, O00585, AAG03773, AAW87589), mouse (O09006, AAG45834) and pig (AAW50886) SLC (encompassing amino acids 46 to 60 of SLC). This motif is inferred to be important for SLC function, namely for binding to chemokine receptors CCR7 and CCR10 and, as a corollary, for its competitive binding with chemokine ELC to said receptors. N-terminal polypeptide fragments of Acrp30R1L and Acrp30R1 comprising said motif non-productively bind to CCR7 and CCR10 and in so doing antagonize SLC and ELC function through CCR7 and CCR10.

[0881] CRPF polypeptide CRPF-1 comprises the amino acid sequence: SHHH (SEQ ID NO:123). CRPF polypeptide CRPF-2A comprises the amino acid sequence:

AANSKVAFSAVRSTNH (SEQ ID NO:124). CRPF polypeptide CRPF-2B comprises the amino acid sequence: AANSKVAFSAVR (SEQ ID NO:125). CRPF polypeptide CRPF-2C comprises the amino acid sequence: STNH (SEQ ID NO:126). CRPF polypeptide CRPF-3 comprises the amino acid sequence: SGSAKVAFSATRSTNH (SEQ ID NO:127). Also preferred are polynucleotides encoding the CRPF polypeptides.

[0886] In a first aspect, the invention features purified, isolated, artificially synthesized, or recombinant CRPF polypeptide that has anti-inflammatory activity. In preferred embodiment, CRPF polypeptide is CRPF-1 polypeptide comprising the amino acid sequence: SHHH (SEQ ID NO:123). In other preferred embodiment, CRPF polypeptide is CRPF-2A polypeptide comprising the amino acid sequence: AANSKVAFSAVRSTNH (SEQ ID NO:124). In other preferred embodiment, CRPF polypeptide is CRPF-2B polypeptide comprising the amino acid sequence AANSKVAFSAVR (SEQ ID NO:125). In other preferred embodiment, CRPF polypeptide is CRPF-2C polypeptide comprising the amino acid sequence STNH (SEQ ID NO:126). In other preferred embodiment, CRPF polypeptide is CRPF-3 comprising the amino acid sequence SGSAKVAFSATRSTNH (SEQ ID NO:127).

[0981] Compounds that suppress or enhance GENSET gene expression can also be identified using *in vivo* screens. In a typical assay, a test compound is administered (e.g. intravenously, intraperitoneally, intramuscularly, orally, or otherwise) to an animal, at a variety of dose levels, and the effect of the compound on GENSET gene expression is determined by comparing the levels of the mRNA or protein encoded by the gene in tissues known to express the gene of interest, e.g., using Northern blots, immunoassays, PCR, etc. Suitable test animals include, but are not limited to, rodents (e.g., mice and rats), primates, and rabbits. Humanized mice can also be used, that is mice in which the endogenous mouse protein is ablated (knocked out) and the homologous human protein introduced using standard transgenic approaches. Such mice thus express only the human form of a protein. Humanized mice expressing only the human GENSET polypeptide can be used to study *in vivo* responses to potential agents regulating GENSET protein or mRNA levels. Such transgenic

animals are useful for dissecting the biochemical and physiological steps of disease, and for development of therapies for disease intervention (see, e.g., Loring, *et al*, 1996).

Please replace pages 1-64 (Sequence Listing) previously submitted to the Patent Office with Applicants' Amendment dated October 9, 2002 with the accompanying Sequence Listing having new pages 1-87.